



UNIVERSITI PUTRA MALAYSIA

**SYNTHESIS, CHARACTERISATION AND BIOLOGICAL ACTIVITIES
OF MIXED-LIGAND COPPER(II) COMPLEXES CONTAINING
SACCHARIN**

THAHIRA BEGUM

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**SYNTHESIS, CHARACTERISATION AND BIOLOGICAL ACTIVITIES OF
MIXED-LIGAND COPPER(II) COMPLEXES CONTAINING SACCHARIN**

By

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**Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in
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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirement for the degree of Master of Science

**SYNTHESIS, CHARACTERISATION & BIOLOGICAL ACTIVITIES OF
MIXED-LIGAND COPPER(II) COMPLEXES CONTAINING SACCHARIN AS
ONE OF THE LIGANDS**

By

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February 2005

Chairman: Professor Karen A.Crouse, PhD

Faculty: Science

New mixed-ligand copper(II) saccharinate complexes of HNNS Schiff bases of S-methyldithiocarbazate, S-benzoyldithiocarbazate, S-2-picolylthiocarbazate and S-4-picolylthiocarbazate were synthesized by reacting $[\text{Cu}(\text{sac})_2(\text{H}_2\text{O})_4] \cdot 2\text{H}_2\text{O}$ with the appropriate Schiff bases in water-ethanol-methanol mixtures. These complexes were characterized by elemental analysis, conductance, magnetic susceptibility, IR and electronic spectroscopic measurements. Magnetic and spectral results for the complexes support either a four or five-coordinate geometry in which the Schiff bases coordinate as NNS tridentate ligands and the saccharinate anion coordinates as a unidentate N-donor ligand. X-ray crystallographic structural analysis of the copper(II)saccharinate complex of S-methyl- β -N-(6-methylpyrid-2-yl)methylenedithiocarbazate shows that the complex has a distorted square-pyramidal structure in which the Schiff base is coordinated to the copper ion as a tridentate NNS chelating agent *via* the pyridine nitrogen atom, the azomethine nitrogen atom and the thiolate sulphur atom. The fourth and fifth coordination positions of the five-coordinate Cu(II) ion are occupied by the imino

nitrogen of the saccharinate anion and oxygen atom of the aqua ligand. X-ray crystallographic structural analysis of the copper(II)saccharinate complex of S-benzyl- β -N-(2-acetylpyridyl)methylenedithiocarbazate shows that this complex has a distorted square-planar structure in which the Schiff base is also coordinated to the copper ion as a tridentate NNS chelating agent with the fourth coordination position of the four-coordinate Cu(II) ion being occupied by the imino nitrogen of the saccharinate anion. The complexes have been evaluated for their biological activities against seven pathogenic microbials and three cancer cell lines, HL-60 (Human myeloid leukemic cells), MCF-7 (Human breast carcinoma cells with positive estrogen receptor) and Caov-3 (Human ovarian adenocarcinoma cancer cells). Most of the complexes exhibit marked cytotoxicity against the cell lines and display moderate activity against pathogenic bacteria and fungi.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia bagi memenuhi keperluan Ijazah Master Sains

**SINTESIS, PENCIRIAN DAN AKTIVITI BIOLOGI BAGI KOMPLEKS
KUPRUM(II) BERLIGAN CAMPURAN YANG MENGANDUNGI SAKARIN
SEBAGAI SALAH SATU LIGAN**

Oleh:

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Kompleks kuprum(II) sakarinat baru yang mengandungi bes Schiff S-metilditiokarbazonat, S-benzilditiokarbazonat, S-2-pikolilditiokarbazonat serta S-4-pikolilditiokarbazonat telah disintesis melalui tindak balas diantara $[\text{Cu}(\text{sac})_2(\text{H}_2\text{O})_4] \cdot 2\text{H}_2\text{O}$ dengan bes Schiff yang sesuai dalam pelarut campuran air-etanol-metanol. Kompleks ini telah dicirikan melalui analisis unsur dan konduktiviti, kerentanan magnetik, pengukuran spektroskopi elektronik dan IR. Kebanyakan kompleks didapati berkoordinatan empat atau lima. Ini dibuktikan melalui nilai kerentanan magnetik dan spektra yang diperolehi. Bes Schiff berkoordinat sebagai ligan tridentat NNS dan ion sakarin berkoordinat sebagai ligan N-penderma unidentat. Analisis struktur hablur sinar X menunjukkan bahawa kompleks kuprum(II) sakarinat bes Schiff S-metil- β -N-(6-metilpirid-2-il) berstruktur piramid segiempat terherot di mana bes Schiff terkoordinat kepada ion kuprum sebagai agen kelat tridentat NNS melalui atom nitrogen piridin, atom nitrogen azometin dan atom sulfur

tiolat. Ligan yang keempat ialah ion sakarinat yang terkoordinat melalui nitrogen imino. Manakala kompleks yang terkoordinat lima, ligan yang kelima ialah air. Analisis struktur hablur sinar X bagi kompleks kuprum(II) sakarinat bes Schiff S-benzil- β -N-(2-asetilpirid-2-il)metilinditiokarbamat menunjukkan bahawa kompleks ini mempunyai struktur segiempat planar terherot dimana bes Schiffnya juga terkoordinat kepada ion kuprum sebagai agen kelat tridentat NNS. Pengkoordinatan yang ke empat bagi ion kuprum(II) diduduki oleh nitrogen imino daripada anion sakarinat. Tujuh patogen mikrob terpilih dan tiga jenis sel kanser, [HL-60 (Sel leukemia myeloid), MCF-7 (Sel kanser payudara dengan reseptor estrogen positif) dan Caov-3 (sel kanser ovari adenocarcinoma)] telah digunakan untuk menilai keaktifan biologi. Kebanyakan kompleks tersebut menunjukkan tanda positif sitotoksik terhadap sel kanser dan menunjukkan keaktifan keatas bakteria dan fungi.

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I certify that an Examination Committee met on 25th February 2005 to conduct the final examination of Thahira Begum on her Master of Science thesis entitled "Synthesis, Characterisation and Biological Activities of Mixed-Ligand Copper (II) Complexes Containing Saccharin" in accordance with Universiti Pertanian Malaysia (Higher Degree) Act 1980 and Universiti Pertanian Malaysia (Higher Degree) Regulations 1981. The Committee recommends that the candidate be awarded the relevant degree. Members of the Examination Committee are as follows:

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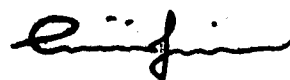
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DECLARATION

I hereby declare that the thesis is based on my original work except for quotations and citations which have been duly acknowledged. I also declare that it has not been previously or concurrently submitted for any other degree at UPM or any other institution.

Thahira Begum

THAHIRA BEGUM

Date: 18.05.2005

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LIST OF ABBREVIATIONS

sac	Saccharinate anion
1D	One-dimensional
FT-IR	Fourier-transform Infrared
B.M	Bohr magneton
LMCT	Ligand to metal charge transfer
MLCT	Metal to ligand charge transfer
DMSO	Dimethylsulphoxide
CD ₅₀	Cytotoxic Dose at 50%
DNA	Deoxyribonucleic acid
HL-60	Human myeloid leukemic cells
MCF-7	Human breast carcinoma cells with positive estrogen receptor
Caov-3	Human ovarian adenocarcinoma cancer cells
CHNS	Carbon,Hydrogen, Nitrogen & Sulphur
NNS	Nitrogen-nitrogen-sulphur
UV/Vis	Ultraviolet/ Visible Spectroscopy
L	Ligand
Bpy	Bipyridine
PPh ₃	Triphenylphosphine
Ap-SBz	2-acetylpyridine Schiff base of S-benzylidithiocarbazate
HSB-1	S-benzyl- β -N-(pyridine-2-yl)methylenedithiocarbazate.
HSB-2	S-benzyl- β -N-(6-methylpyrid-2-yl)methylenedithiocarbazate.

HSB-3	S-benzyl- β -N-(di-2-pyridylketone)methylenedithiocarbazate.
HSB-4	S-benzyl- β -N-(2-acetylpyridyl)methylenedithiocarbazate.
HSB-5	S-benzyl- β -N-(2-benzoylpyridyl)methylenedithiocarbazate.
HSM-2	S-methyl- β -N-(6-methylpyrid-2-yl)methylenedithiocarbazate.
HSM-3	S-methyl- β -N-(di-2-pyridylketone)methylenedithiocarbazate.
HSM-4	S-methyl- β -N-(2-acetylpyridyl)methylenedithiocarbazate.
HSM-5	S-methyl- β -N-(2-benzoylpyridyl)methylenedithiocarbazate.
HS2P-1	S-2-picolyl- β -N-(pyridine-2-yl)methylenedithiocarbazate.
HS2P-3	S-2-picolyl- β -N-(di-2-pyridylketone)methylenedithiocarbazate.
HS2P-5	S-2-picolyl- β -N-(2-benzoylpyridyl)methylenedithiocarbazate.
HS4P-1	S-4-picolyl- β -N-(pyridine-2-yl)methylenedithiocarbazate.
HS4P-2	S-4-picolyl- β -N-(6-methylpyrid-2-yl)methylenedithiocarbazate.
HS4P-3	S-4-picolyl- β -N-(Di-2-pyridylketone)methylenedithiocarbazate.
HS4P-4	S-4-picolyl- β -N-(2-acetylpyridyl)methylenedithiocarbazate.
HS4P-5	S-4-picolyl- β -N-(2-benzoylpyridyl)methylenedithiocarbazate.
[Cu(SB-1)(sac)]	Copper(II) Saccharinate Complex of S-benzyl- β -N-(pyridine-2-yl)methylenedithiocarbazate
[Cu(SB-2)(sac)]	Copper(II) Saccharinate Complex of S-benzyl- β -N-(6-methylpyrid-2-yl)methylenedithiocarbazate
[Cu(SB-3)(sac)]	Copper(II) Saccharinate Complex of S-benzyl- β -N-(di-2-pyridylketone) methylenedithiocarbazate
[Cu(SB-4)(sac)]	Copper(II) Saccharinate Complex of S-benzyl- β -N-(2-acetylpyridyl)methylenedithiocarbazate
[Cu(SB-5)(sac)]	Copper(II) Saccharinate Complex of S-benzyl- β -N-(2-benzoylpyridyl)methylenedithiocarbazate

[Cu(SM-2)(sac)]	Copper(II) Saccharinate Complex of S-methyl-β-N-(6-methylpyrid-2-yl)methylenedithiocarbazate
[Cu(SM-3)(sac)]	Copper(II) Saccharinate Complex of S-methyl-β-N-(di-2-pyridylketone)methylenedithiocarbazate
[Cu(SM-4)(sac)]	Copper(II) Saccharinate Complex of S-methyl-β-N-(2-acetylpyridyl)methylenedithiocarbazate
[Cu(SM-5)(sac)]	Copper(II) Saccharinate Complex of S-methyl-β-N-(2-benzoylpyridyl)methylenedithiocarbazate
[Cu(S2P-1)(sac)]	Copper(II) Saccharinate Complex of S-2-picolyl-β-N-(pyridine-2-yl)methylenedithiocarbazate
[Cu(S2P-2)(sac)]	Copper(II) Saccharinate Complex of S-2-picolyl-β-N-(6-methylpyrid-2-yl)methylenedithiocarbazate
[Cu(S2P-3)(sac)]	Copper(II) Saccharinate Complex of S-2-picolyl-β-N-(di-2-pyridylketone)methylenedithiocarbazate
[Cu(S2P-4)(sac)]	Copper(II) Saccharinate Complex of S-2-picolyl-β-N-(2-acetylpyridyl)methylenedithiocarbazate
[Cu(S2P-5)(sac)]	Copper(II) Saccharinate Complex of S-2-picolyl-β-N-(2-benzoylpyridyl)methylenedithiocarbazate
[Cu(S4P-1)(sac)]	Copper(II) Saccharinate Complex of S-4-picolyl-β-N-(pyridine-2-yl)methylenedithiocarbazate
[Cu(S4P-2)(sac)]	Copper(II) Saccharinate Complex of S-4-picolyl-β-N-(6-methylpyrid-2-yl)methylenedithiocarbazate
[Cu(S4P-3)(sac)]	Copper(II) Saccharinate Complex of S-4-picolyl-β-N-(di-2-pyridylketone)methylenedithiocarbazate
[Cu(S4P-4)(sac)]	Copper(II) Saccharinate Complex of S-4-picolyl-β-N-(2-acetylpyridyl)methylenedithiocarbazate
[Cu(S4P-5)(sac)]	Copper(II) Saccharinate Complex of S-4-picolyl-β-N-(2-benzoylpyridyl)methylenedithiocarbazate
[Cu(sac) ₂ (OH ₂) ₄].2H ₂ O	Copper(II) Saccharinate

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B14	FT-IR Spectrum of [Cu(SM-3)(sac)]	150
B15	FT-IR Spectrum of HSM-4	151
B16	FT-IR Spectrum of [Cu(SM-4)(sac)]	151
B17	FT-IR Spectrum of HSM-5	152
B18	FT-IR Spectrum of [Cu(SM-5)(sac)]	152
B19	FT-IR Spectrum of HS2P-1	153
B20	FT-IR Spectrum of [Cu(S2P-1)(sac)]	153
B21	FT-IR Spectrum of [Cu(S2P-2)(sac)]	154
B22	FT-IR Spectrum of HS2P-3	155
B23	FT-IR Spectrum of [Cu(S2P-3)(sac)]	155
B24	FT-IR Spectrum of [Cu(S2P-4)(sac)]	154
B25	FT-IR Spectrum of HS2P-5	156
B26	FT-IR Spectrum of [Cu(S2P-5)(sac)]	156
B27	FT-IR Spectrum of HS4P-1	157
B28	FT-IR Spectrum of [Cu(S4P-1)(sac)]	157
B29	FT-IR Spectrum of HS4P-2	158
B30	FT-IR Spectrum of [Cu(S4P-2)(sac)]	158
B31	FT-IR Spectrum of HS4P-3	159
B32	FT-IR Spectrum of [Cu(S4P-3)(sac)]	159
B33	FT-IR Spectrum of HS4P-4	160
B34	FT-IR Spectrum of [Cu(S4P-4)(sac)]	160
B35	FT-IR Spectrum of HS4P-5	161
B36	FT-IR Spectrum of [Cu(S4P-5)(sac)]	161



EQUATIONS

No.		Page
1	$[\text{ML} \cdot \text{Cl}] + \text{DMSO} \longrightarrow [\text{ML}(\text{DMSO})]^+ + \text{Cl}^-$ <p>$[\text{M} = \text{Ni(II), Cu(II), Zn(II) and Sn(II), L} = \text{NNS}]$</p>	48
2	$[\text{M}'(\text{NNS})\text{Cl}_2 \cdot \text{H}_2\text{O}] + 3\text{DMSO} \longrightarrow [\text{M}'(\text{NNS})(\text{DMSO})_3]^{2+} + 2 \text{Cl}^- + \text{H}_2\text{O}$ <p>$[\text{M}' = \text{Cr(III), Sb(III)}]$</p>	48

CHAPTER I

INTRODUCTION

Saccharin – Structure and Historical Background

The structure of saccharin (sac), 1,2-benzisothiazoline-3-(2H)one 1,1-dioxide or *o*-sulphobenzoimide is shown in Figure 1.

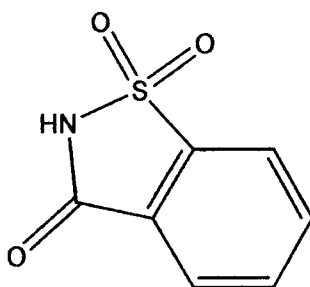


Figure 1: Structure of Saccharin

Saccharin is the world's oldest low-calorie sweetener and is 500 times as sweet as sugar. It was discovered in 1879 by researchers lead by Prof. Ira Remsen at John Hopkins University. Initially, consumption of saccharin was primarily confined to diabetics who could then enjoy sweetened foods without the extra calories, or glucose reaction associated with many sweeteners (Watkins(a), 2004). Subsequently, because of sugar rationing during the World Wars, a strong need for a sugar substitute both in the U.S and Europe developed and this need was met by saccharin. Even after World War II, saccharin continued to be used as a popular alternative to sugar, as people's interest in weight control developed. Its usefulness remained significant until the 1970s. Due to the synergistic and functional properties of saccharin, and its low cost, it remains a valuable

low-calorie sweetener today. Saccharin continues to be important for a wide range of low-calorie and sugar-free food and beverage applications (Watkins(a), 2004).

Saccharin has been the subject of extensive scientific research. It is one of the most studied food ingredients. Although evidence indicates that saccharin is safe for human consumption, there has been controversy over its safety. The basis for the controversy was the indication of the development of bladder tumors in male rats fed high doses of sodium saccharinate. Consequently, a ban was imposed on saccharin and its usage, although the male rats used in the study were fed the human equivalent of the sodium saccharinate in hundreds of cans of diet soft drink a day for a lifetime (Watkins(b),2004). However, extensive research on human populations has established no association between saccharin and cancer even at consumption levels above that of the average user of less than one ounce of the sweetener each year (Watkins(c), 2004).

The scientific data supporting safety of saccharin include the following:

1. Extensive research on human populations has established no association between saccharin and cancer. More than 30 human studies have been completed and indicate saccharin's safety at human levels of consumption.
2. In fourteen single-general animal studies involving several species of animals, saccharin was not shown to induce cancer in any organ, even at exceptionally high doses.